VCd versus VRd in Newly Diagnosed Multiple Myeloma: Matched Real-World Analysis from the Balkan Myeloma Study Group (BMSG)

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Abstract

As induction therapy, VRd demonstrated superior efficacy in terms of response rates over VCd, but not in PFS and OS in the real-world setting. Long-term outcomes are driven by effective consolidation and use of maintenance. VCd induction remains a reasonable option for patients for which VRd may not be feasible or well-tolerated and could find a niche in novel combinations.

Background: Bortezomib, dexamethasone and cyclophosphamide (VCd) remains a popular regimen, due to its activity and low toxicity, while bortezomib, lenalidomide and dexamethasone (VRd) is widely used in US and Europe; both are combined with anti-CD38 monoclonal antibodies but VCd and VRd have not been compared directly in adequately powered prospective trials. **Aim:** We compared the outcomes of 1216 patients treated with VCd ($N = 690$) or VRd ($N = 526$) in a real-world setting. **Results:** Patients treated with VCd had more often severe renal dysfunction, ISS-3 disease, hypercalcemia, elevated LDH, anemia, thrombocytopenia, poor performance while VRd-treated were older and received less often autologous transplant but more frequently maintenance but the duration of induction was similar. VRd was associated with substantially higher overall response and CR/VGPR rates to induction($P < .001$) and improved PFS and OS in univariate analysis, especially among patients with standard risk disease, without renal dysfunction and in the elderly; however, in multivariate analysis there was no significant difference in either PFS or OS. In patients strictly matched 1:1 for major prognostic variables (188 in each group, total $N = 376$), the superiority of VRd in terms of responses rates and depth of response was confirmed, but without significant PFS or OS difference. **Conclusion:** VRd is a more active induction regimen than VCd, although use of maintenance with lenalidomide may dilute the PFS or OS benefit. VCd induction remains an option in special circumstances. With the implementation of monoclonal antibodies, VCd backbone can be considered for patients without access to or who do not tolerate VRd.

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Introduction

Multiple myeloma (MM) is a complex and heterogeneous malignancy for which an unprecedented increase in the treatment options has occurred in the past 20 years. Primary therapy for newly diagnosed symptomatic myeloma (NDMM) has prominently featured bortezomib-based triplets as the main backbone regimen.[1] Bortezomib with dexamethasone and cyclophosphamide (VCd or CyBorD) has emerged as a widely employed regimen, since about 2009,[2] that is characterized by significant activity and a favorable toxicity profile. Its efficacy and safety have been particularly noteworthy in patients with renal dysfunction and within resource-constrained healthcare settings, contributing to its popularity as a frontline therapeutic option. In parallel, the integration of bortezomib with lenalidomide and dexamethasone (VRd) has gained significant traction, especially in North America and Europe, supported by compelling evidence from pivotal phase 3 studies[3-5] which positioned VRd as a robust induction therapy prior to high-dose melphalan and autologous stem cell transplantation (HDM-ASCT). Additionally, a prospective comparison of VRd against lenalidomide and dexamethasone (Rd) in patients with nonimmediate transplant intention, the SWOG S0777 trial, have led to the approval of this regimen for patients who are not transplant candidates.[6,7] International guidelines, from the European Hematology Association (EHA) and the European Society for Medical Oncology (ESMO),[1] recommend VRd as one of the preferable options for primary therapy, in both transplant eligible and ineligible patients. In contrast, VCd is considered as an alternative (secondary) option if other, preferable options, are unavailable, but only for patients eligible for ASCT, while, due to the lack of data, it is not proposed for non-ASCT eligible patients.[1] However, in clinical practice VCd is a commonly used regimen also among elderly patients, due to its favorable toxicity profile. While VCd and VRd contain the Vd backbone, an IMiD (lenalidomide) or an alkylator (cyclophosphamide) may offer advantages in specific settings especially since MM is such heterogeneous disease. The comparative evaluation of VCd and VRd has primarily been explored through retrospective studies, focusing mostly on transplant eligible patients[8-11] and only small randomized studies[12,13] has compared their short-term efficacy. Few prospective comparisons of VTd to VCd indicate superiority of VTd[14] but again, they mostly explore short-term efficacy (i.e. responses rates) and also VTd and VRd do have significant differences in their toxicity profile. Today, compelling evidence support the use of quadruplets with the addition of anti-CD38 antibodies to bortezomib-based triplets.[15-19] While combinations of anti-CD38 antibodies with a PI (either bortezomib or carfilzomib) and lenalidomide seem to offer substantial rates of complete responses and high rates of undetectable minimal residual disease (MRD), there are still combinations of these antibodies with VCd which are explored in prospective studies, especially in vulnerable populations (such as those with severe renal dysfunction, plasma cell leukemia, AL amyloidosis, etc.).[20]

In this context, our study aims to compare outcomes of patients treated initially with VCd or VRd, in a real-world setting, based on data from the Balkan Myeloma Study Group (BMSG), including both transplant eligible and transplant ineligible patients. To provide a more balanced analysis we further conducted a matched analysis of VCd and VRd treated patients.

Patients and Methods

We identified 1911 consecutive patients with newly diagnosed multiple myeloma, who were diagnosed and treated in centers participating in the Balkan Myeloma Study Group with either VCd or VRd. We restricted the study period in patients that started therapy from January 2016 to December 2022, to reduce the effect of availability of fewer options before 2016. Patients who started VCd or VRd and after 1-2 cycles changed to the other regimen for reasons other than disease progression/lack of response were excluded from the analysis. Finally, the analysis included 1216 patients that fulfilled the criteria and had the minimum required data to be included in the analysis (690 treated with VCd and 526 treated with VRd).

The data have been prospectively or retrospectively collected in each institution, depending on local policy, and have been uploaded and maintained in a central database (database of the BMSG). An approval for the collection of data, upload to the central server of the BMSG, analysis and publication has been obtained by each institutes' Ethics Committee/Scientific Board.

Baseline characteristics included demographic information (age, sex, race), laboratory values (hemoglobin, creatinine, calcium, albumin, lactate dehydrogenase (LDH), beta-2- microglobulin (β2M), isotype, M-spike and serum free light chains) and the presence of cytogenetic abnormalities. All were recorded from the time of diagnosis. Also, data regarding date of diagnosis, treatment initiation, use of HFM-ASCT, consolidation and/or maintenance therapy, best response to induction therapy, dates of progression and death were collected.

Statistical Analysis

Comparisons for categorical variables among different groups (VCd vs. VRd) were made with the chi-square test, using Fisher's exact test when appropriate. Overall survival (OS) was measured from the date of treatment initiation until the date of death or date of last follow up. Time to event curves were plotted with the method of Kaplan and Meier, and comparisons among groups were made using the log rank test. We performed subgroup analyses in groups of special interest: elderly (>65 years), HDM and HDM-treated, patients with severe RI (ie, eGFR<30 ml/min/1.73 m^2), those with high risk cytogenetics, ISS-3 and R2-ISS-high risk. For multivariate analysis, factors associated with time to event were introduced into a Cox proportional hazards model. For the matched analysis, the groups were matched 1:1 for age, country, ISS-3 stage, cytogenetics, HDM and maintenance use. Matching was performed by using "Case-Control Matching" feature in IBM SPSS v25 software (SPSS Inc., Chicago, IL), which was also used for the statistical analysis.

Results

Patient Demographics and Disease Characteristics

The analysis encompassed a cohort of 1216 NDMM patients from the BMSG database, with 690 receiving VCd and 526 receiving VRd. An initial comparison of patient demographics revealed significant differences between the 2 groups. Patients treated with

Table 1 Characteristics of the Patients Treated With VCD and With VRd as Induction Regimens

	Unmatched Groups		
	VCd $N = 690$	VRd $N = 526$	*P*-Value
Age > 65 years	41.5%	49%	.009
eGFR < 30 ml/min/1.73 m2	26.4%	9.2%	< .001
Hypercalcemia (serum Ca > 11 mg/dl)	25.5%	13.5%	< .001
PLT < 130 k/μL	9.8%	6.6%	.088
HgB < 10 gr/dl	44.9%	35.4%	.001
ECOG PS 3-4	17%	11.5%	.021
ISS ($N = 1176$)	23.1% / 25.3% / 51.6%	37.2% / 34.5% / 28.3%	< .001
HR cytogenetics ($N = 1022$)	22.3%	20%	.366
LDH high ($N = 1194$)	24.3%	16.3%	.001
R-ISS ($N = 1100$)	7.4% / 76.7% / 16.2%	18.8% /71.1% / 10.1%	< .001
R2-ISS ($N = 977$)	11.2%/20.5%/52.2%/15%	19.9%/30.1%/ 37.1%/12.1%	< .001
HDM with ASCT	44.5%	33.1%	< .001
Maintenance	45%	70.1%	< .001
ORR (in ITT population) (95% CI)	77.5% (75.5-79.5)	86% (84-88_	< .001
ORR (in evaluable patients) (95% CI)	88% (86-90)	97% (95.5-98.5)	< .001
CR/VGPR (95% CI)	54.5% (48-54)	69% (65-73)	< .001
PFS months median (95% CI)	33 (28-38)	44.9 (34-55)	< .001
PFS months median in non-HDM treated (95% CI)	16.6 (14.1-19.1)	33.2 (27-39.3)	< .001
PFS months median in HDM treated (95% CI)	59.5 (47.5-71.5)	NR(NE)	< .001
4-year PFS in HDM treated (95% CI)	57% (54-60)	72% (68-76)	.003
4-year OS (95% CI)	69% (67-71)	78% (76-80)	.002
4-year OS in Non-HDM treated (95% CI)	51% (48-54)	69% (63-72)	< .001
4-year OS in HDM treated (95% CI)	85% (82-88)	93% (90-96)	.035

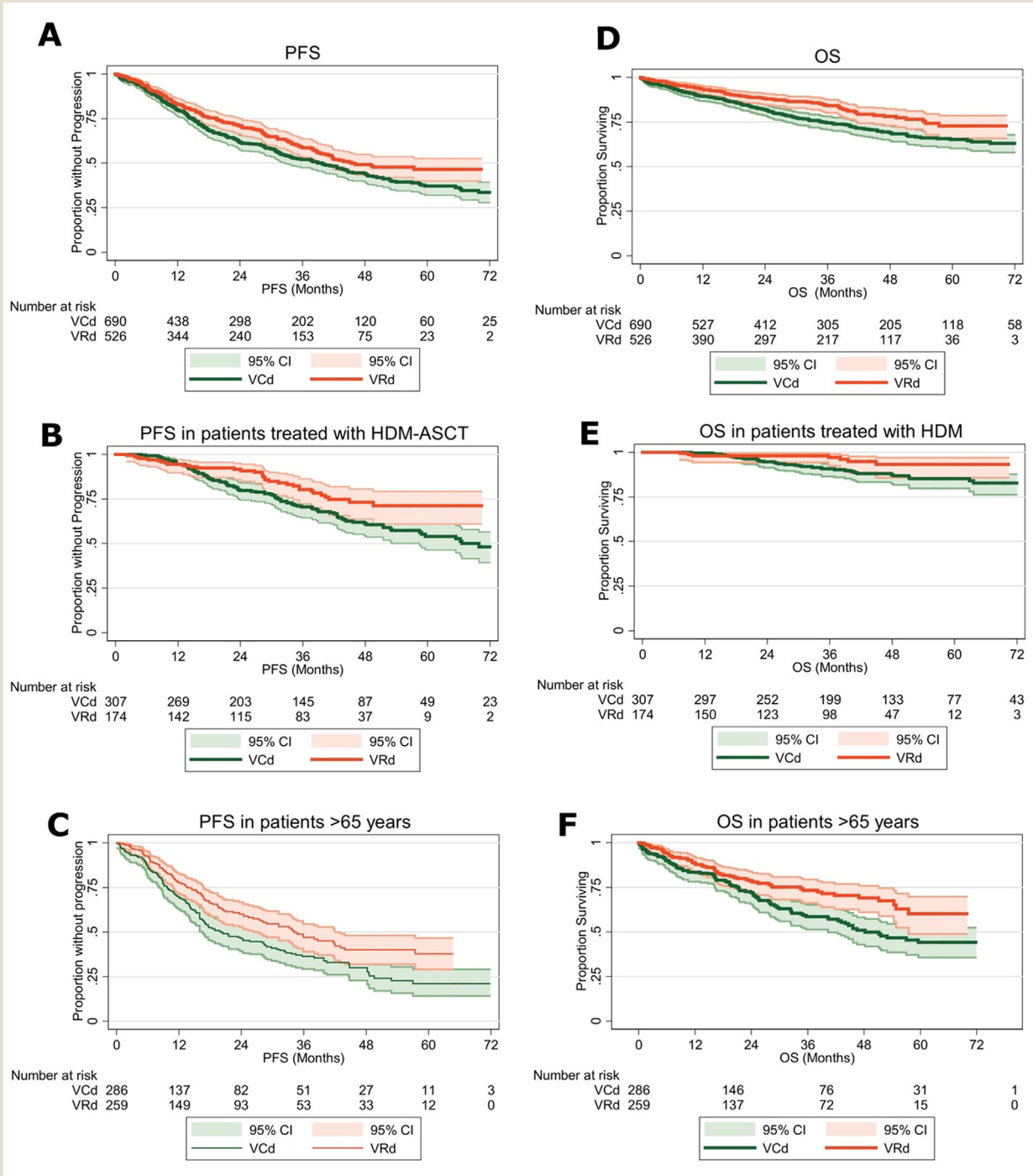
VCd were less frequently aged over 65 years (41% vs. 49%, $P = .009$), exhibited a higher incidence of hypercalcemia (25.5% vs. 13.5%, $P < .001$), of severe renal dysfunction (eGFR < 30 ml/min/1.73 m2) (26% vs. 9%, $P < .001$), elevated serum LDH (24% vs. 16%, $P = .001$), lower platelet counts (< 130 K/uL) (10% vs. 7%, $P = .08$), anemia (with Hgb < 10 gr/dl) (45% vs. 35%, $P = .001$), and a higher prevalence of ECOG performance status > 2 (17% vs. 11%, $P = .021$), compared to VRd treated. Furthermore, ISS stage distribution differed significantly between the two groups, with VCd patients presenting a higher proportion of ISS-3 disease (51% vs. 28%, $P < .001$). The duration of induction with VCd and VRd was 5.8 and 6 months for non-HDM treated and 3.9 and 4 months for HDM-treated patients. Treatment-related differences were also significant: consolidation with HDM was utilized more frequently in VCd-treated patients (44% vs. 33% of VRd-treated patients, $P < .001$). Post-HDM consolidation was used in 40% and 37% of patients respectively ($P = .4$) but maintenance therapy following induction or consolidation was administered less frequently in VCd versus VRd-treated patients (in 45% vs. 70%, respectively ($P < .001$). The characteristics of the 2 groups are shown in Table 1.

Unmatched Comparison of Response Rates and Survival Outcomes

Early mortality rate (< 3 months) was 3% for VCd and 2% for VRd-treated patients. Among all patients (intention to treat population) the ORR was 77.5% for VCd and 86% for VRd treated patients ($P < .001$). Among patients evaluable for response after induction (605 treated with VCd and 468 treated with VRd), VRd-treated patients exhibited a higher overall response rate (≥ PR) compared to VCd-treated patients (97% vs. 88% of evaluable patients, $P < .001$); this difference was also extended to depth of responses, with VRd-treated patients achieving CR/VGPR rates of 69% compared to 54% for VCd ($P < .001$).

The median follow-up was 41 months for VCd and 35 months for the VRd group. The median progression-free survival (PFS) favored VRd, at 44 months, compared to 28 months for VCd treated patients ($P = .001$) (Figure 1A). In the subgroup of patients that received transplant, the 4-year PFS was 57% months for VCd and 72% for VRd-treated patients ($P = .003$) (Figure 1B). In a sensitivity analysis, use of maintenance was associated with significantly longer PFS and OS in both groups ($P < .001$ in each group). In patients > 65 years (median age was 71 years for VCd and 72

Figure 1 Unmatched comparison of survival outcomes: (A) progression-free survival (PFS) of VCd versus VRd in the whole population (B) those that received HDM with ASCT (C) patients age > 65 years. (D) OS of VCd versus VRd in the whole population (E) those that received HDM with ASCT (F) patients age > 65 years.



years for VRd) the median PFS was 18 versus 33 months ($P = .001$) (Figure 1C).

We further compared the efficacy of the 2 regimens within the subgroup of ASCT-treated patients that also received lenalidomide maintenance: the 4-year PFS rate was 62% for VCd compared to 4-year PFS rate of 75% for VRd (median not reached at 3 years of follow up)($P = .006$).

The median OS has not been reached for either group and the 4-year OS rate for VCd treated patients was 69% and for the VRd-treated group was 78% ($P = .002$) (Figure 1D). The 4-year OS for those that received ASCT was 85% in the VCd-treated and 93% in the VRd group ($P = .035$) (Figure 1E). In the subgroup of patients who received lenalidomide-maintenance after ASCT the 4-year OS rate was 88% for VCd and 93% for the VRd group ($P = .184$). In patients > 65 years the 4-year OS was 52% versus 69% ($P = .003$) (Figure 1F). In the non-ASCT treated patients the 4-year OS rate was 51% and 69% respectively for VCd and VRd ($P < .001$). Table 1 shows PFS and OS with their respective 95% CIs.

We then performed a multivariate analysis, incorporating major prognostic factors and treatments (HDM and use of maintenance) that differed between the two groups. We evaluated two models, one with ISS, LDH and high-risk cytogenetics as independent variables and one that incorporated instead R2-ISS. VRd was independently associated with a higher probability of achieving CR/VGPR over VCd in 2 different models (OR: 2.22, 95% CI 1.53-3.21, $P < .001$ and OR: 2.23, 95% CI 1.48-3.38, $P < .001$). However, in multivariate analysis for PFS, VRd induction was not independently associated with longer PFS in the two models, and neither with OS. Use of maintenance with lenalidomide and of HDM with ASCT were the main drivers of improved PFS and OS in our cohort of myeloma patients (Supplemental Table 1).

Subgroups

We further explored the efficacy of the two regimens in predefined subgroups of special interest: patients with severe RI (eGFR < 30 ml/min/m^2), those with high risk (HR) cytogenetics [ie, t(4;14), t(14;16), del17p)], patients with ISS-3 disease and those with R2-ISS high-risk disease (which also incorporates amp/add1q21 in the evaluated cytogenetic abnormalities). Cytogenetics and R2-ISS were not available in all patients. Table 2 and Figure 2A-F shows the results of the analysis in the various subgroups.

Matched Group Analysis

Since the two groups differed significantly in their characteristics and also had major differences in the major prognostic drivers identified in the multivariate analysis, and in order to decrease bias, we performed an analysis that included only patients matched 1:1 for age > 65 years, country, ISS-3 stage, cytogenetics risk (high vs. standard), use of HDM and of maintenance. This matched group analysis included 376 patients (188 in each group). Table 3 shows the characteristics of the two groups in this analysis which were significantly more balanced than in the total population. In this cohort, VRd was associated with higher response rates over VCd and corresponding CR/VGPR rates after induction. The median follow-up was 36 months for the VCd and 35 months for the VRd group. The 4-year PFS rand OS rates were not significantly different between the two groups (Figure 3 and Table 3). Posthoc power analysis, with an alpha of 0.05, indicated that the analysis had a 97.7% power to detect CR/VGPR rate difference, 79% for PFS difference and 45% for OS difference. In the subgroup of ASCT-treated patients, in the matched cohort, the 4-year PFS rates was 70% (95% CI 64-76) for VCd and 71% (95% CI 65-77) for VRd ($P = .854$). The estimated 4-year OS rates were 91% for VCd vs. 93% for VRd, $P = .846$). Among the nontransplant subgroup (also aged > 65), the median PFS was 21 (95% CI 12-45) months for VCd versus 37 (26-43) months for VRd ($P = .036$) and 4-year OS was 60% (95% CI 53-67) versus 70% (95% CI 63-77) ($P = .288$). In a multivariate analysis in the matched cohort, the most important factors associated with better PFS were achievement of CR/VGPR at end of induction, use of HDM-ASCT and of maintenance, absence of anemia and of thrombocytopenia, and with better OS were achievement of CR/VGPR at end of induction, use of HDM-ASCT and of maintenance (Supplemental Table 2).

Discussion

In this large retrospective study, VRd was associated with higher rates and deeper responses after induction when compared to VCd, however, the impact of this induction regimen was less pronounced regarding PFS and OS. The characteristics of the patients differed significantly in the two groups treated with the different regimens; we adjusted for these variables in both multivariate analysis and in a matched-group comparison, which revealed that although there is still a superiority of VRd over VCd induction, the impact on PFS and OS may be less pronounced, especially when maintenance is part of the therapy. We have included in our analysis only patients that started treatment after 2016, when more treatment options became available and maintenance with lenalidomide became standard. Importantly, both the outcomes of patients treated with VRd in our cohort were similar to those reported from prospective clinical trials,[3-5] as well for VCd-treated patients, which had similar outcomes to patients treated in prospective studies using this induction regimen and lenalidomide maintenance[21] (Supplemental Table 3).

Consistent with previous prospective clinical trials and retrospective studies, VRd demonstrated superior response rates, with a high proportion of patients achieving complete (CR) or very good partial response (VGPR) compared to VCd, at the end of induction. This finding underscores the potent antimyeloma activity of the combination of a proteasome inhibitor (bortezomib) with an IMiD (lenalidomide). However, we also observed the substantial effect of maintenance therapy with lenalidomide, in both VRd and VCd treated patients and, thus, there was no significant difference in the PFS and OS between induction regimens, when adjusting for use of HDM and of maintenance. Nonetheless, we have to note that fewer patients that receive VRd induction will require salvage therapy before they receive HDM and maintenance, and this cannot be captured in the current analysis, potentially downsizing the difference between the two regimens.

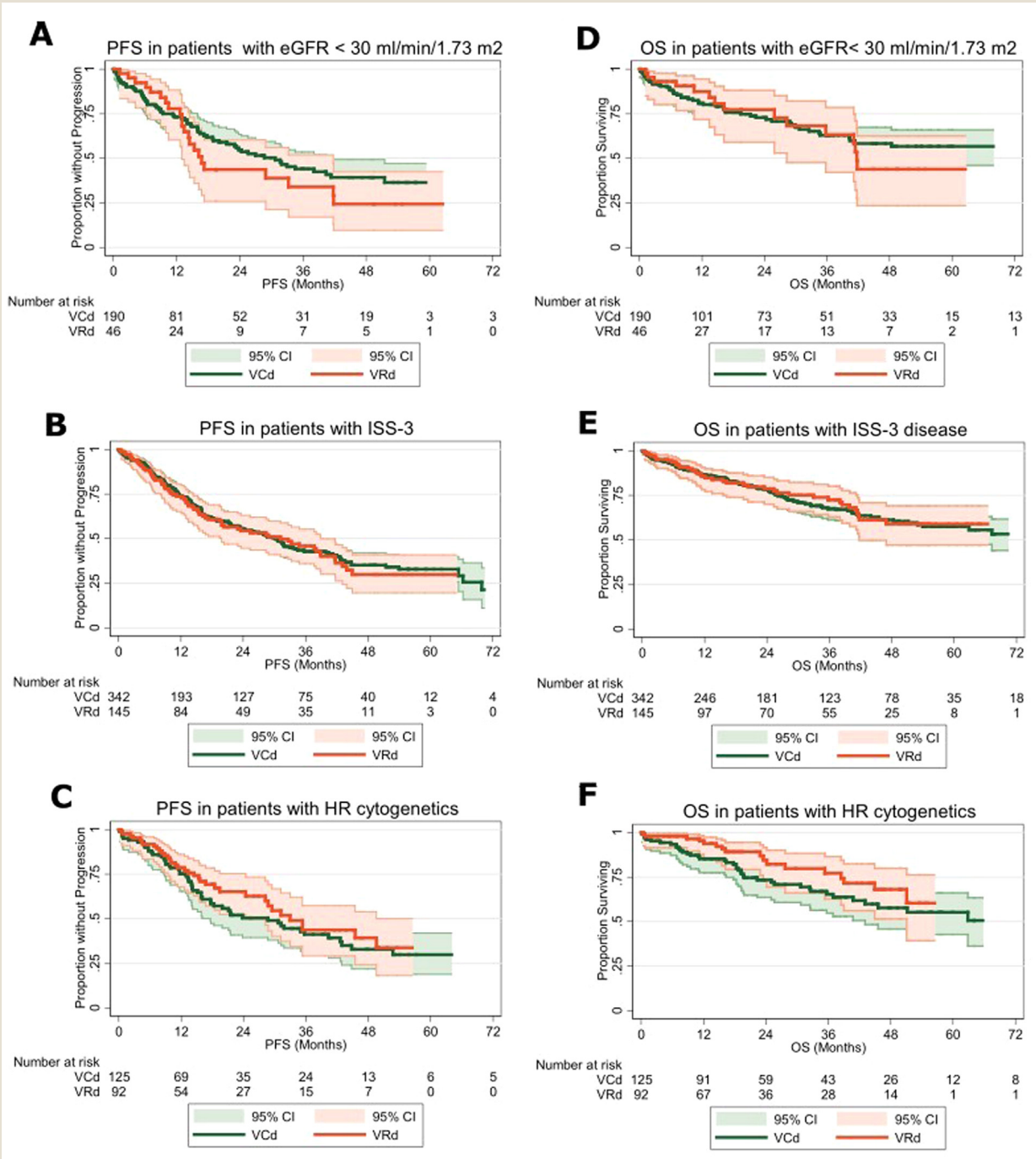
By analyzing the outcomes of patients in specific subgroups (Table 2) it is interesting to note that among patients over the age of 65 and non-ASCT eligible, VRd was associated with improved PFS (both in the unmatched and matched comparisons), proba-

Table 2 Outcomes of Patient Subgroups; 95% CIs Are Provided in Parentheses

	VCd	VRd	*P*-Value
Age > 65 years	*N* = 286	*N* = 259	
ORR	82% (79-85)	97% (95-99)	< .001
CR/VGPR	43% (38-48)	65% (59-71)	< .001
PFS(median in months)	18 (13-23)	33 (26-38)	.001
4-year OS	52 (48-56)	69 (65-73)	.003
Age < 65 years	*N* = 404	*N* = 267	
ORR	91% (89-93)	96% (93-98)	.034
CR/VGPR	53% (49-57)	71%(65-77)	.001
4-year PFS	41 (31-39)	58(50-66)	.01
4-year OS	78 (76-80)	84 (81-87)	.011
eGFR < 30	*N* = 190	*N* = 46	
ORR[a]	88% (83-92)	97% (90-100)	.001
CR/VGPR[a]	46% (40-52)	68% (54-80)	.021
PFS(months)	25.6 (16-35)	16 (13-20)	.415
4-year OS	56% (51-61)	41% (30-52)	.744
eGFR > 30	*N* = 500	*N* = 480	
ORR[a]	87% (83-92)	94% (90-99)	.234
CR/VGPR[a]	54% (49-59)	68% (66-70)	.001
PFS(months)	32 (28-35)	46 (32-58)	.001
4-year OS	71% (69-73)	80%(78-82)	.012
ISS-3 (ISS available in *N* = 1176)	*N* = 342	*N* = 145	
ORR	86% (80-92)	95% (89-98)	.009
CR/VGPR	47% (42-54)	66% (56-74)	.001
PFS (median - months)	28 (22-33)	28 (17-40)	.940
4-year OS	62 (59-65)	59 (53-65)	.789
ISS-1/2	*N* = 321	*N* = 368	
ORR	90% (86-94)	97% (95-99)	< .001
CR/VGPR	60% (55-65)	70% (67-71)	.012
4-year PFS	49%(46-52)	58(55-61)	.016
4-year OS	77 (74-80)	85 (83-87)	.037
HR cytogenetics (cytogenetics available in *n* = 1022)	*N* = 125	*N* = 92	
ORR	87% (83-91)	97% (94-100)	.021
CR/VGPR	55% (47-61)	77% (75-61)	.002
PFS (median - months)	29 (17-40)	32 (26-40)	.379
4-year OS	58% (54-62)	67% (61-73)	.124
SR cytogenetics	*N* = 436	*N* = 369	
ORR	89% (87-91)	97% (95-99)	< .001
CR/VGPR	53 (49-56)	66 (64-68)	< .001
4-year PFS	41% (38-44)	52% (48-56)	.001
4-year OS	73% (70-76)	79%(75-83)	.074
R2-ISS-High (R2-ISS available in *n* = 977)	*N* = 62	*N* = 40	
ORR	81% (75-87)	94% (86-100)	.084
CR/VGPR	37% (26-47)	83% (71-94)	< .001
PFS(months)	15 (5-24)	19.5 (11-28)	.433
4-year OS	55% (48-63)	53% (41- 65)	.761

[a] Evaluable at the end of induction.

Figure 2 Outcomes of subgroups of special interest: (A) PFS of VCd versus VRd in patients with severe RI (eGFR < 30 ml/min/m2), (B) with ISS-3 disease (C) patients with high risk (HR) cytogenetics [ie t(4;14), t(14;16), del17p)], (D) OS of VCd versus VRd in patients with severe RI (eGFR < 30 ml/min/m2), (E) with ISS-3 disease (F) patients with high risk (HR) cytogenetics [ie, t(4;14), t(14;16), del17p)].



bly driven by continuous lenalidomide. In the subgroup of patients with severe RI (ie, eGFR < 30 ml/min/m^2) VCd was associated with numerically longer PFS and OS (without statistical significance). We do not have data about renal response in these patients, but our data indicate that VCd is a reasonable option for patients with severe renal dysfunction, and potentially with a more favorable toxicity profile than VRd, due to the need for adjustment of lenalidomide dose for renal impairment.[20,22] In patients character-

Table 3 Characteristics of the Patients in the Matched Groups

	VCd $N = 188$	VRd $N = 188$	*P*-Value
Male / Female	49%/ 51%	48.5%/51.5%	.844
Age > 65 years[a]	38.3%	38.3%	1.000
Age > 75 years	11.2%	14.6%	.303
eGFR < 30	22%	12%	.007
Hypercalcemia	33.5%	16.6%	< .001
PLT < 130	8%	7%	.706
HgB < 10	42.6%	40.8%	.701
PS 3-4	12.2%	12.4%	.977
ISS[a]	29.6% / 32% / 38.3%	35.9% / 25.7% / 38.3%	.263
R2-ISS ($N = 290$)	15.6% / 22.5% / 46.3% / 15.6%	16.6% / 24.5% / 41.4% / 17.8%	.850
HR cytogenetics[a]	24%	24%	1.000
LDH high	22%	22%	.979
HDM[a]	47%	47%	1.000
Maintenance[a]	62%	62%	1.000
ORR	91.8% (88-95)	99% (96-100)	< .001
CR/VGPR	60.4% (51-70)	71.4% (64-77)	.027
4-year PFS	50% (45-65)	55% (50-60)	.184
4-year OS	79% (75-83)	81% (77-85)	.517

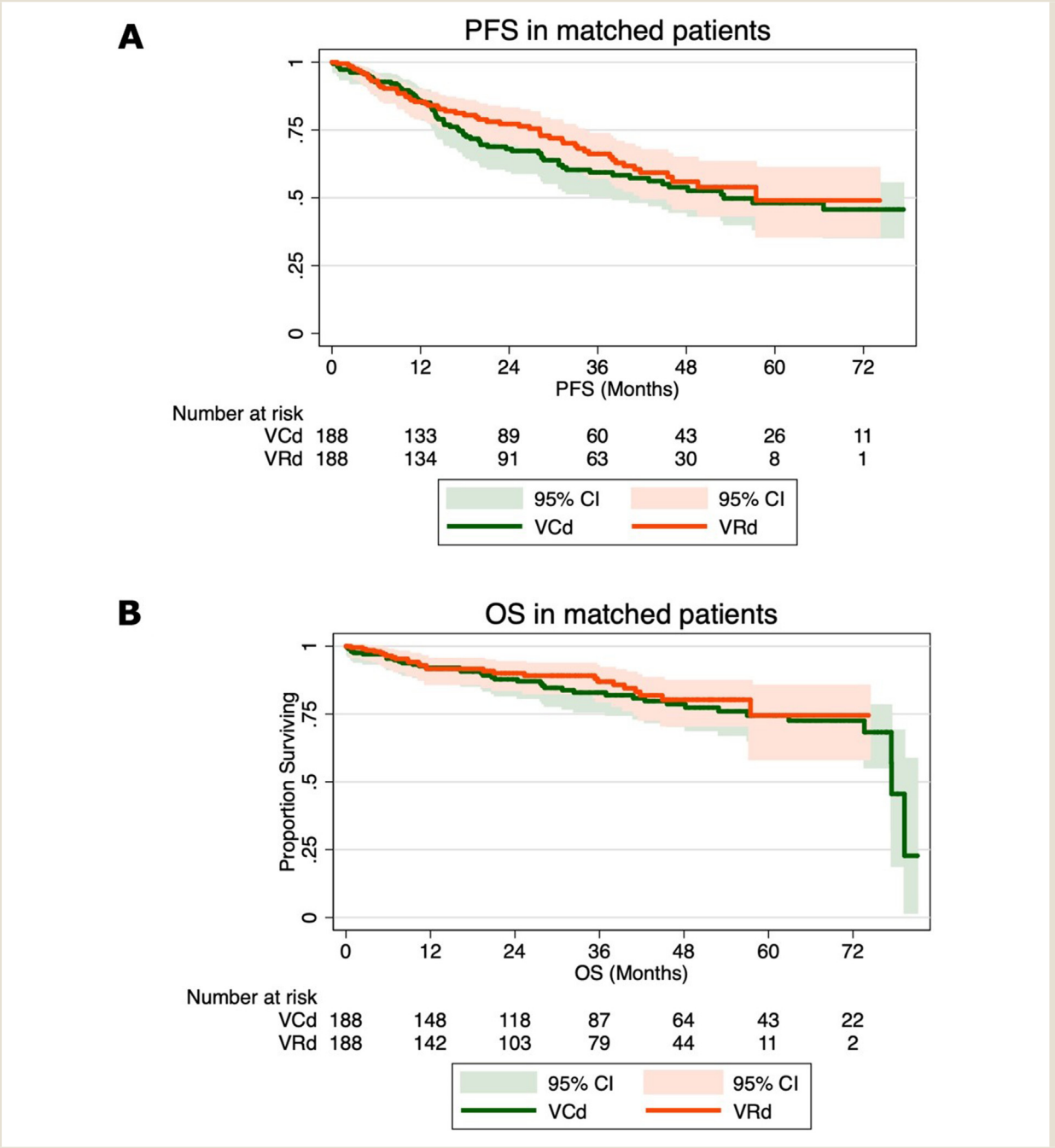
[a] These were matching variables.

ized by high-risk features (such as those with HR cytogenetics, ISS-3 disease, R2-ISS high risk) VCd is performing poor and is probably a suboptimal treatment; VRd was associated with better but still poor results, and the outcomes of such patients remained poor, emphasizing the need for more effective approaches. Currently, intensive regimens, either quadruplets[15,16,18] or quintuplets,[17] that contain anti-CD38 monoclonal antibodies and second-generation PIs, seem to offer a significant improvement in the rates of MRD negative remission and prolonged PFS. Among standard risk patients that received HDM and maintenance, the outcome is quite favorable, with high rates of PFS and OS at 4 years, which are indicative of the progress that has been made in the treatment at first line, the impact of continuous therapy and the increasing options at relapse.

A prospective comparison of the two regimens in an adequately powered study is unlikely, and today regimens that incorporate anti-CD38 monoclonal antibodies are becoming the standard of care.[15] Nevertheless, the backbone of these regimens remains VRd[15] or, for special populations VCd.[23,24] In addition, for many countries and regions, VCd remains a less expensive regimen, although lenalidomide is becoming much cheaper (but not in all countries). Thus, comparing VRd with VCd has clinical value, and provides insights on the clinical and biological heterogeneity of myeloma and its management. A difference of our retrospective study over previously published ones is that we performed a matched analysis, aiming to mitigate baseline imbalances, that offered a nuanced perspective on the comparative effectiveness of the two regimens. VRd maintained superiority in response rates but the absence of a significant difference in PFS and OS raises intriguing questions regarding concurrent versus sequential use of regimens, as pointed by the effect of lenalidomide maintenance after VCd. This question cannot be resolved with the current study. Despite differences in response rates, the ultimate impact on longer-term outcomes (PFS and OS) is influenced by factors beyond the depth of initial conventional response, including minimal residual disease, later events, patient frailty, and future treatment options, emphasizing the complexity of myeloma biology and the need for evaluation of treatment outcomes beyond traditional response metrics.

The current study, as a retrospective, real-world data driven analysis, has inherent limitations. First, the regimens were not standardized in terms of dosing, schedule, and planned duration of induction. Second, the administration of maintenance was not standardized. The variations in treatment patterns, including the utilization of high-dose melphalan (HDM) and maintenance, further exemplify the divergent clinical contexts in which VCd and VRd were applied. These variations highlight the complexity of decision-making in the real-world setting, where patient-specific factors, disease characteristics, and resource considerations play pivotal roles in treatment selection. Finally, our effort to strictly match the patients resulted in a significant reduction of the number of patients that could enter the matched-group analysis; however, there was still a significant number of patients to be analyzed ($N = 376$, 188 in each group). Another limitation that has to be acknowledged is the reactively short follow up of the matched cohort which may not allow to capture long-term differences.

Figure 3 Outcomes analysis in the matched groups ($N = 188$ in each group). PFS (A) and OS (B) in the matched cohort.



Conclusion

In conclusion, VRd demonstrates superior efficacy in terms of response rates over VCd, but not in terms of PFS and OS in a matched-groups comparison in the real-world setting. VCd remains a clinically relevant regimen and a reasonable option for patient for which VRd may not be feasible or well-tolerated. Additionally, VCd could find a niche in novel combinations, aligning with the evolving landscape of myeloma therapies.

Clinical Practice Points

- VRd demonstrates superior efficacy in terms of response rates over VCd, associated with signifcantly higher overall and CR/VGPOR rates after induction.
- Long term outcomes with VCd and VRd, such as PFS and OS, do not seem to be signfcantly different when autologous trasnplanation and lenalidomide maintenance are used.

- Among high risk patients both regimen are associated with poor outcomes, indicating the need for new approaches and startegies.
- Although VRd is superior in short term outcomes, VCd remains a reasonable option for patient for which VRd may not be feasible or well-tolerated.

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CRediT authorship contribution statement

Efstathios Kastritis: Writing – original draft, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Meral Beksac:** Writing – review & editing, Resources, Data curation. **Sorina Nicoleta Badelita:** Writing – review & editing, Resources, Data curation. **Eirini Katodritou:** Writing – review & editing, Resources, Data curation. **Jelena Bila:** Writing – review & editing, Resources, Data curation. **Emmanouil Spanoudakis:** Writing – review & editing, Resources, Data curation. **Guldane Cengiz Seval:** Writing – review & editing, Resources, Data curation. **Zorica Cvetkovic:** Writing – review & editing, Resources, Data curation. **Olivera Markovic:** Writing – review & editing, Resources, Data curation. **Selami Koçak Toprak:** Writing – review & editing, Resources, Data curation. **Dimitra Dalampira:** Writing – review & editing, Resources, Data curation. **Daniel Coriu:** Writing – review & editing, Resources, Data curation. **Zoi Bezirgiannidou:** Writing – review & editing, Resources, Data curation. **Mario Pirsic:** Writing – review & editing, Resources, Data curation. **Toni Valkovic:** Writing – review & editing, Resources, Data curation. **Iulia Ursuleac:** Writing – review & editing, Resources, Data curation. **Aleksandra Sretenovic:** Writing – review & editing, Resources, Data curation. **Angeliki Sevastoudi:** Writing – review & editing, Resources, Data curation. **Josip Batinic:** Writing – review & editing, Resources, Data curation. **Sinziana Barbu:** Writing – review & editing, Resources, Data curation. **Maria Roussou:** Writing – review & editing, Resources, Data curation. **Maria Gavriatopoulou:** Writing – review & editing, Resources, Data curation. **Evangelos Terpos:** Writing – review & editing, Resources, Data curation. **Meletios A. Dimopoulos:** Writing – review & editing, Resources, Data curation.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clml.2024.08.007.

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